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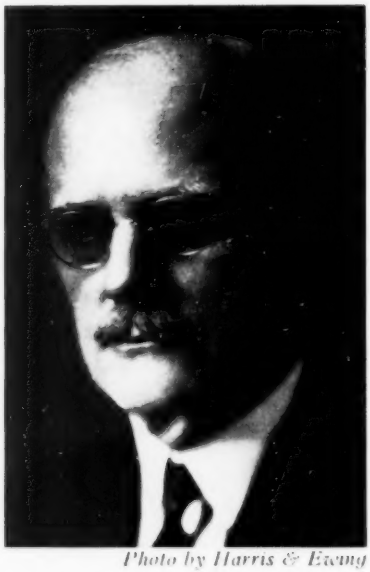

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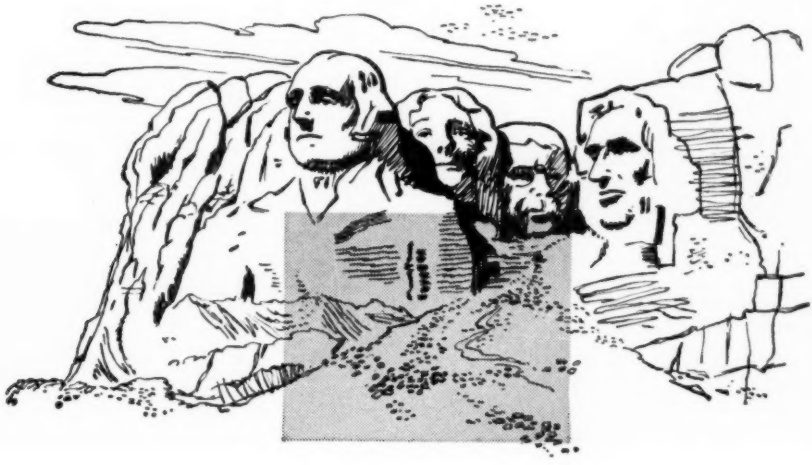

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OUR COVER

AMBROSE SOUDER HUNSBERGER
1873-1949

ON July 8th, at the Chestnut Hill Hospital, one who had long been the symbol of professional pharmacy, hereabouts, passed to his eternal reward! Dr. Ambrose Hunsberger, a graduate of the class of 1908 of Medico Chirurgical College, Department of Pharmacy, had throughout his life given a devotion to the best interests of pharmacy and because of his personality and sincerity he maintained, even to the lengthening shadows of his career, a vivid interest in his field and a mastery of his responsibilities, making his name known and respected in every aspect of public health services in his City, in his State and indeed, throughout the Union.

From a biographic source in the historical archives of the Philadelphia College of Pharmacy and Science, his various services throughout the years are herewith quoted:

Mr. Hunsberger was a past president of the National Association of Retail Druggists, the Pennsylvania Pharmaceutical Association, the Philadelphia Association of Retail Druggists, the Philadelphia Branch American Pharmaceutical Association and past Secretary of the latter association—succeeding a former intimate associate, the late Martin I. Wilbert—serving in this position of three terms when he was elected President. He acted as Chairman, Section Commercial Interest, American Pharmaceutical Association at the Philadelphia meeting in 1926 and also served as Local Convention Chairman at the same meeting. In the same year he served as Chairman, Committee on Allied Pharmaceutical Interest, Sesqui-Centennial Exhibition, of Philadelphia. In 1929 he served as Chairman, House of Delegates of the American Pharmaceutical Association.

He took an active part in the reorganization of the Pennsylvania Pharmaceutical Association providing for a full time Secretary and the establishment of the Central Office. He also assisted in the reorganization of the Philadelphia Association of Retail Druggists, taking an active part in developing interest in the acquisition of its own building as well as in taking over the publication of its organ, the P. A. R. D. Bulletin. He served as Advertising Director for three years during which time the Bulletin was converted into a sub-

stantial asset of the P. A. R. D. He took an active part in the expansion program of the Philadelphia College of Pharmacy and Science, which culminated in the erection of the new college building.

He served as Assistant Supervisor (Permissive) in the Bureau of Industrial Alcohol for over five years, and by reason of his knowledge of the legitimate uses of alcohol and medicinal liquors he was able to safeguard the interests of the Government and to smooth the way for law-abiding permittees.

Mr. Hunsberger served the pharmacists of the Nation in the following capacities: Chairman Executive Committee, National Association of Retail Druggists; President, Drug Trade Bureau Public Information; Chairman, Business Research Committee, National Conference of Pharmaceutical Research; Member, Advisory Committee, Druggists Research Bureau; Member, Committee on Costs of Medical Care; Vice-President, National Drug Trade Conference; Member Council, American Pharmaceutical Association, Secretary and Trustee, Philadelphia College of Pharmacy and Science (succeeding the late Professor Joseph P. Remington as Trustee).

In recognition of his many contributions to the profession of Pharmacy, the Philadelphia College of Pharmacy and Science conferred upon him the degree of Master in Pharmacy in 1922. He operated a highly ethical prescription store at 1600 Spruce Street, Philadelphia, Pa., for many years and also conducted a branch store at Souderton, Penna.

His affiliations with fraternal, social and professional associations were numerous. Mention is made here of a few: Penn Athletic Club, Kappa Psi, Masonic Order, St. Mark's Church, Pennsylvania Historical Society, Pennsylvania Genealogical Society, Academy of Fine Arts, Academy Political and Social Science, Philadelphia Clinical Society, Associate Fellow, American Medical Society, etc.

The foregoing can only briefly enumerate the services which this able and dignified pharmacist gave to his own calling and to the commonwealth as well. And yet the record, splendid as it is, cannot adequately picture the good influence that he had all through his life on young men serving in his establishment and, indeed, on thousands of others who were glad to look upon him as a shining example of intelligent devotion to his profession and to his fellowmen!

IVOR GRIFFITH.

E D I T O R I A L

ANTIHISTAMINICS OVER THE COUNTER

THE approval by the Food and Drug Administration of certain antihistaminics for sale to the public was both a surprise and a shock to many people. This action by the FDA has been hailed by some as a logical step and fully warranted, while others contend that it should not have been done.

The decision to release these drugs for over the counter sale was based on experiments which would seem to indicate that a few of them are sufficiently devoid of side reactions, such as drowsiness, to make them safe for public consumption. Those antihistaminics so far placed in this category are Thonzylamine, Pyranisamine and Chlorprophenpyridamine. Whether, indeed, these three are the only ones suitable for use by the laity is certain to be strongly debated, since it will not be easy for manufacturers of other antihistaminics to accept this seeming superiority on the part of their competitors' products.

That there will be a hurried scramble to get these new "cold cures" on the market is certain. The common cold is looked upon by the public as "public enemy number one," and no really effective medication has been on the market, until now, which would do more than afford some symptomatic relief. The advertising for these new remedies is certain to be vigorous and as high pressure as the Federal Trade Commission will allow. Some of the old stand-by cold remedies will be forced into this new field if they are not to lose much of their sales.

Just what the long term results will prove concerning this new therapeutic approach is not at all clear. If one believes the projected advertising of some of these new products, it would appear that the cold will soon be as rare as small-pox, but these advertisements are undoubtedly a gross over-statement of fact. It does seem that the antihistaminics taken at the proper time do much to abort, or at least give symptomatic relief from the early symptoms of, the cold. The

exact mechanism whereby they accomplish this is not entirely clear. Some believe it is because the virus causes the release of histamine in the tissues and that the antihistaminics thus block and prevent the typical histamine reactions.

One cannot help but wonder what the result of large scale use of these drugs will be. It is one thing to have drugs used on prescription and quite another to have them made generally available over the counter. By the use of simple mathematics it is easy to see why some inherent toxicity of these drugs might entirely escape detection until they were used on a mass scale. Presumably they have been proven safe, but it will not be certain until they have stood the test of billions of doses taken by millions of people. Then we shall know, and let us hope that the answer will not be that they are dangerous.

The medical profession, as might be expected, is almost uniformly opposed to the sale of these drugs to the public. Physicians, by their very nature of training, tend to be conservative since they well know the dangers of precipitous action. It has been pointed out by a number of physicians that these drugs often cause drowsiness, although those approved, as has been stated, are claimed to be devoid of this side-effect. The warning has also been sounded that the frequency of drug idiosyncrasy with these new materials is not too well known. We must admit that there is considerable merit in the warnings of medical practitioners, but there is also, without doubt, some small lack of objectivity in their pronouncements. If these drugs are proved highly efficient in preventing or treating an early cold, much of the demand for medical attention during the winter months would be minimized. The physician, after all, is a human being, and he would not appreciate having his importance and the need for his services diminished. We have often wondered what the reaction of the medical profession would be if someone were to develop a drug the use of which would absolutely eliminate all possibility of infection. Would the medical profession acclaim its discovery or would there be secret resentment that unfair competition was being exercised? We pose this question not with sarcasm toward our medical colleagues but simply to point out that they, too, are human.

It will be interesting to observe the continuing development in this field. Will the drugs cause accidents by promoting drowsiness?

Will chronic toxicity develop or will they prove to be entirely safe and the real means of combatting the common cold? Will their use, over a period of time, lower the threshold of response to histamine and make some persons even more susceptible to its effects? No one knows the final answer, and only time will give us the full story. It is our prediction that, in the end, these drugs will prove far less efficient than the extravagant claims now made by their proponents and far less dangerous than described by conservative medical opinion. It is, however, our personal opinion that it might have been better to gain more experience with these drugs before releasing them for uncontrolled sale.

L. F. Tice.

STUDIES ON ALCOHOL-SOLUBLE FUNGISTATIC AND FUNGICIDAL COMPOUNDS

VI. A CRITICAL REVIEW OF FUNGISTATIC AND FUNGICIDAL TEST METHODS

By Kurt A. Oster and Milton J. Golden *

IN 1945, the Council on Pharmacy and Chemistry of the American Medical Association (1), in a report entitled "The War and Dermatophytosis," stated: "It is urgent that a standard test be established promptly" for the in vitro testing of antifungal compounds. It stated further that no serious attempt had been made to resolve the various methods which had been advanced previously—and which were all open to criticism—into one standard test, as the phenol coefficient test had been set up for bacterial disinfectants and antiseptics. The Council made the reservation, however, that fungus growth conditions differ considerably from those of bacteria, and that there are differences among the growth conditions of various pathogenic fungus species.

This review will be limited to the present test methods for those fungi which cause dermatophytosis, the four chief representatives of which are (1) *Trichophyton mentagrophytes*, (2) *Trichophyton purpureum*, (3) *Epidermophyton inguinale*, and (4) *Monilia albicans*. As has been shown by Emmons (2), *Trichophyton rosaceum* should not be included in such tests, since it is not pathogenic for humans.

Clinical Tests

Before reviewing the existing laboratory test methods for antifungal substances, one should first clearly define what should be expected of in vitro fungistatic and fungicidal tests. It can be easily seen that the ideal test, the 100 per cent duplication of actual clinical conditions, can be only approximated but not attained. All efforts should therefore be directed to the closest possible simulation of those

* From the Research Laboratories of McKesson and Robbins, Inc., Bridgeport, Conn. Read in part at the Gordon Research Conference A. A. A. S. on Medicinal Chemistry, Colby Junior College, August, 1948.

clinical conditions. On the other hand, we might argue that if laboratory tests are of no convincing value, why not limit our tests to clinical studies? But if laboratory assays for antifungal substances possess certain shortcomings, the so-called clinical tests have shown a good deal of prejudice, confusion and lack of objectivity. These drawbacks of the clinical screening of antifungal substances lie partly in the variable nature of the dermatophytoses themselves and partially in problems innate to clinical testing. It is unfortunate that we cannot retrace our steps and treat the same infection over and over again with a variety of compounds, but each time under identical clinical conditions.

Therefore, clinical evaluation has to rely on the statistical approach, which is often most unsatisfactory considering the frequent remissions found in dermatophytosis. Furthermore, clinical studies are often handicapped by the prevalent attitude of the patient who usually does not consider dermatophytosis to be sufficiently severe to warrant repeated examinations by a physician. Recurrences are frequently a cause for a change of physicians.

There remains institutional or group material for clinical testing purposes. But here again, the variety of the case material is rather limited. In most cases one deals with minor lesions. The attention drawn to proper foot hygiene may cause remissions, and the evaluation of the test material is rather difficult.

The Council on Pharmacy and Chemistry of the American Medical Association (1) has set up twelve rules for the clinical testing of antifungal compounds which, if observed in the medical literature, would do away with a goodly number of reports and, consequently, unsatisfactory preparations. Recently, an eminent dermatologist stated, "There is not one preparation on the market which will not cure *some* case of athlete's foot." The clinical testing of antifungal substances, therefore, must be relegated to a secondary position as far as timing is concerned. Preliminary screening should be accomplished by properly initiated in vitro tests which afford a definite indication of the relative efficacy of the substances under test. Those which are screened out as effective in these in vitro test should be subjected subsequently to clinical trials which, naturally, have the last word about the qualities of such a compound. An example may be given to that effect.

In a series of fifty-five compounds tested by us, four were found to possess outstanding in vitro qualities. It was necessary, however, to discard the top three compounds as clinically impractical, since they caused extensive skin irritation on patch testing (3). The clinical test is not to be dispensed with, by any means, in the development of a new antifungal compound found effective in the laboratory, but it can not be used for screening purposes.

Definition of Terms

Much of the present confusion regarding in vitro tests for substances used in dermatophytosis therapy may be attributed to the loose usage of the terms "fungistatic" and "fungicidal." Fungistatic action of a substance indicates its growth-preventing effect on a fungus culture, so long as it is in contact with the organisms. Fungicidal action, on the other hand, designates the killing effect of a compound on a fungus culture after contact for a limited period of time, making certain that the compound is completely removed from the culture, following the contact time, and that the basic structure of the colony has not been altered, either by the compound or by the test method.

If one makes these definitions the criterion for any suggested test method, he would exclude, as far as in vitro test methods are concerned, all compounds which form permanent chemical complexes with the fungus proteins such as various mineral salts, and those which destroy the fungus itself, such as strong acids or bases. Likewise, all fungicidal methods which alter the basic structure of the colony would be excluded by this definition. Further, if one considers that the multitude of antifungal substances are water insoluble and alcohol soluble, a number of suggested in vitro test methods—especially those designed to test fungicidal qualities would fall by the wayside when this strict definition is applied to them.

Fungistatic Test Methods

Let us examine critically the in vitro methods suggested for the testing of antifungal substances. Probably the first laboratory method of significance suggested in this country was that by Schamberg and Kolmer in 1922 (4). For the determination of fungistasis, the accurately diluted test substance (in aqueous solution if possible)

is incorporated in Sabouraud's agar slants. The freshly isolated fungus is seeded, and the tube is incubated at room temperature. A number of dilutions of the drug should be used, and each test should be repeated to insure accuracy. This method, which in its suggested form is mainly applicable to water soluble compounds, has been used with minor modifications by a multitude of authors.

In 1931, McCrea (5) suggested that a slightly modified Schamberg and Kolmer method be adopted as the standard fungistatic test. Lewis and Hopper's (6) excellent book on medical mycology mentions only the Schamberg and Kolmer method of testing fungistatic power.

Let us examine the limitations of this test method more closely. The test is designed mainly for use with water soluble compounds. In their paper on the fungicidal power of phenol derivatives, Woodward, Kingery and Williams (7) complained about this shortcoming and attempted to circumvent it by dissolving their compounds in alkali (thereby changing the pH) or in dilute alcohol. This change in solvents makes the test an individual procedure for each substance tested. At one time one has water; at another time, alkali; and at a third time, various dilutions of a proper solvent. This creates an embarrassing situation for anyone trying to assay fungistatic compounds on a really comparative basis.

We have modified the Schamberg and Kolmer method (4) in such a way as to be applicable to alcohol-soluble compounds without violating its underlying principle (8). In view of the fact that alcohol itself possesses minor fungistatic properties, it was necessary to limit the quantity of alcohol incorporated in the agar to 0.1 cc., an amount which exerted no noticeable fungistasis on plates containing 20 cc. of Sabouraud's agar. The original concentration of the test substance in alcohol was thereby diluted two hundred times. The surfaces of the plates were streaked with a ten-day-old culture of the test organism, and the plates were incubated for two weeks, after which time the presence or absence of growth was noted. The highest dilution of the test material which completely inhibited the growth of fungi after a two-week incubation period was regarded as the critical fungistatic dilution.

The original Schamberg and Kolmer (4) method does not incorporate serum in the agar. It is common knowledge that some

of the apparently most effective antifungal substances are inhibited by the presence of proteins. Therefore, the Sabouraud's agar medium used in this method should contain at least 10 per cent serum to ascertain a possible protein effect. It is understood that the 10 per cent value is chosen arbitrarily and does not signify that 10 per cent serum is equivalent to the protein content of the human skin.

This fungistatic test method is very valuable in the testing of volatile compounds. Its shortcomings are that the test reveals only one value at which the substance is either fungistatic or not fungistatic. Nothing is learned of the essential activity of a compound at those concentrations where fungistasis is progressing and at those concentrations where fungistasis is leveling off to reach a constant ceiling.

This particular information may be gained by another fungistatic in vitro test method, the so-called agar cup plate method, originally described by Reddish in 1929 and the United States Department of Agriculture Circular No. 198, for determining bacteriostasis and adapted for fungistatic testing by Burlingame and Reddish in 1939 (9). The serum agar is prepared by adding 2 cc. of sterile normal horse serum to 18 cc. of Sabouraud's agar, which has been melted and cooled to 40 degrees. The agar is poured into a 9 centimeter Petri dish, and, when hardened, the entire surface of each plate is streaked with a ten-day-old culture of the test organism. A 2 centimeter cup is cut from the center of the plate with a sterile cork borer, and approximately 0.8 cc. of the test substance is pipetted into the cup in 95 per cent alcohol. The fungistatic activity of a given compound is indicated by a cleared zone around the cup. Solvent controls with 95 per cent alcohol showed that the fungistatic effect of the solvent in this method is minimal. This method, as originally described by Burlingame and Reddish (9), was applied by these authors for a single concentration of the fungistatic substance, and single values for therapeutic preparations are reported in the medical literature.

To learn more of the activity of any given drug, it is standard procedure in pharmacology to establish its dosage response. We applied this principle of dosage response to the agar cup plate test for fungistasis and in this way tried to determine the actual fungistatic activities of various compounds. The plant pathologists have

employed the dosage response in their spore germination tests using the LD_{50} or LD_{90} at various concentrations of fungistatic compounds as their yardstick (10). It may be said here that this method is excellent, provided the test organism has suitable spores; Sclerotinia fructicola and Macrosporium sarcinaeforme fulfill these requirements admirably. However, the trichophytons and the epidermophytons, which constitute the majorty of fungi pathogenic for the human skin, have small spores, and the test did not prove successful in our hands with the use of these organisms.

Principally, it may be stated that the test organisms for in vitro testing, in order to be considered of practical value in medical mycology, should be organisms which cause human pathology and not plant pathology. The individual susceptibility of a fungus to a given substance varies considerably. The two fields are too widely separated today by the therapeutic qualities expected of an effective antifungal compound to be comparable. The advantage which the slide germination method claims to have over the agar cup plate method is that of the elimination of agar from the procedure. The distilled water utilized by the former method is naturally free of the adsorptive colloidal material encountered in agar.

To explain the contact of the water-insoluble antifungal compound with the spores, two theories have been put forth by the plant pathologist; one, the Oligodynamic Theory, and two, the so-called Suicide Theory (11). The first theory postulates that there is a sub-lethal dose of the chemical in a solubility equilibrium with the drop of water. The spore absorbing part of this dissolved material in its lipoid layers depletes the water of the material, and the deficit is made up by further dissolving the chemical from the undissolved depot. The other possibility considered is that, during the process of germination, the spores excrete some metabolic products into the water, such as amino acids, which in their turn serve as solubilizers of the test substance. Even in this method, a theoretical carrier is necessary to explain the penetration of the antifungal substance into the spore. In the agar cup method we encounter the same condition and problem of penetration, only on a larger scale. We deal with the same problem of penetration, but, at least, we start by adding the test substance in a dissolved form and not as a solid, as the plant pathologist does. Whatever the mechanism of penetration through

the agar may be, is that phenomenon an indication of the ability of the antifungal substance to penetrate such material as epidermis? The answer to this question, which constitutes the major attack on the agar cup plate method, is neither a simple "Yes" nor "No." Penetration through epidermis and through agar are certainly not identical, even if the agar does contain some proteins. The method claims only to afford some indication of eventual penetration, and that it certainly does.

We believe that this question of penetration through agar, paralleling penetration through epidermis, has been as much overstressed by those on the positive side of the problem as by those on the negative side. The clearance zone around the agar cup, as we like to call it, is for our purposes merely a measure of the fungistatic activity of a given compound, and by measuring several clearances at different dosages, we obtain the slope of this activity by the dosage response curve. One should not read too much into one laboratory test and then condemn it, because it does not furnish all the desired information at once.

In any method designed to evaluate various products, a yardstick is neded as a quantitative expression of the observed values. In bacteriological testing, the phenol coefficient of Rideal and Walker (12) is in common use. Thus far, no such common denominator has been found for the testing of antifungal substances. Emmons (2) suggested a test employing the phenol coefficient for antifungal substances, but his method has major shortcomings. It can be applied only to water soluble substances designed for determining the action of compounds on floors and the like.

We suggested an expression of fungistatic activity and called it the activity coefficient (8). We adopted the method used in assaying penicillin where a clear zone of 22 millimeters diameter is the expression of one unit of penicillin. Paralleling this evaluation, a standard of 5 millimeters clearance of the agar plate at a 1 per cent concentration of any given substance was arbitrarily chosen by us as the activity 1. Using *Trichophyton mentagrophytes* as the test organism, the concentration, at which a compound exhibited 5 millimeter clearance, divided into the Figure 1 gave the fungistatic activity coefficient of this particular substance. This method avoids reference to a standard fungistatic compound and refers only to a

given area of radius segment clearance with a given organism, which demonstrated extremely reproducible qualities on culturing in our hands.

A new means of expressing fungistasis by measuring the activity coefficient derived from dosage response curves is herewith suggested. Thus, the standardization of the activity of one substance against the activity of another, which might act by a completely different mechanism is avoided. The standard conditions are those of medium and of culture.

For the sake of completeness, mention is made here of some minor modifications of the agar cup plate method. Taft, in 1939 (13), suggested a delayed cup plate by flooding a second layer of agar over the first layer. Since the dermatophytons are chiefly aerobic organisms, this modification is not desirable. It smothers the growth. Incorporating a conidial suspension in the agar rather then streaking it with a culture has no decided advantage in making this more cumbersome method more desirable. The use of the penicup method for alcohol soluble fungistatic compounds, as suggested by Hillegas and Camp in 1945 (14) produced only irreproducible results in our hands. The solvent would seep beneath the penicup cylinder, and the results were dependent on the resultant flooding of the surface with the solution. The method is well applicable to water soluble substances.

A different approach to the testing fungistasis is the method described by Sharlit (15), who incorporates the chemical under test in a collodion membrane. It was claimed that these tests results would be an expression of fungicidal power. At best, however, it will demonstrate only fungistasis.

Fungicidal Test Methods

This brings us then to the field of testing for fungicidal activity. The situation in this field, unfortunately, is quite different from the just described fungistatic tests. It is here that most of the present confusion originates. The importance of testing for fungicidal power cannot be overstressed, since it is with this test that the eventual clinical performance of a new fungicide may be predicted. Let us then go back to our original definition of a fungicidal test, which stated three basic conditions: (1) Contact of fungus culture and

fungicide for a limited period of time, (2) complete removal of the fungicide from the fungus culture by a suitable washing step, and (3) the condition that the basic structure of the colony should not be altered either by the compound or by the test method.

If we examine some of the suggested test methods in the light of the last postulate, we find that most of these methods definitely alter the basic structure of the fungus culture. Fungi grow differently from bacteria, and to force their testing into a sort of a straight-jacket simply because the test methods are used on bacteria is driving the issue of unification of test procedures too far. A mold consists of hyphae, matted together into a mycelium, and a variety of spores, conidia, or chlamydospores. The growth of the fungus colony occurs by either one of these components. Most tests favor the conidial phase for testing with consequent neglect of the hyphal forms and the chlamydospores. It is not absolutely certain which form of growth is responsible for human pathogenicity. It may be that all three forms share in the infectiousness and in the individual spread of dermatophytosis. Therefore, it seems only logical to test the fungi as fungi and not as bacteria. For this reason, we are opposed in principle to those methods which artifically break up the mycelia with glass beads, as the methods suggested by Schamberg and Kolmer (4) and the subsequent modification by McCrea (5) and by Klarmann, Sternov, and Gates (16). The same objection holds also for the method suggested by Emmons (2).

In 1932, Smyth and Smyth (17) suggested a new fungicidal test method. They took pieces of the entire matted fungus culture, supposedly containing all three major forms of fungus growth, and tested on these little blocks the action of pine oils. The test compound was washed out with 95 per cent alcohol, and the alcohol was then removed by rinsing with saline. The age of the test culture ranged from 1 to 2 months. This method was modified and popularized by Burlingame and Reddish in 1939 (9). Various articles have appeared since that time making use of the Burlingame and Reddish method for testing fungicidal compounds. The variation suggested by Burlingame and Reddish consisted principally in enlarging the size of the test block and in leaving the agar together with the culture and in eliminating the rinsing step in 95 per cent alcohol, substituting instead a longer washing period in watery broth.

The reasons for this were merely stated but not substantiated by suitable experimentation.

We have thoroughly investigated this fungicidal method (18) and have found after careful scrutiny of the steps involved in performing this technique that it reveals the following shortcomings, which are most evident when alcohol soluble fungicides are employed: (1) The test culture is not sufficiently aged; (2) The contact time of the fungicide with the culture is overly long; (3) No serum has been incorporated in the medium to detect any eventual protein effect; and (4) a water-insoluble, alcohol-soluble fungicide cannot be removed from the culture disk by shaking it in watery broth.

Burlingame and Reddish (9) recommended a culture age of five days. Microscopic examination of cultures of Trichophyton mentagrophytes reveals that hyphal structure predominates in a 5-day-old culture. After 10 days, an abundance of microspores or microconidia can be observed, while a 15-day old culture exhibits many thick-walled chlamydospores. These time variations in the basic culture characterists should be afforded careful consideration in any fungicidal test method. Since these test conditions should most closely simulate the human pathological picture found in dermatophytosis, the test culture to be used should contain most of the various morphologic structures of fungus growth and reproduction. Use of the relatively immature 5-day-old culture does not fulfill this need. McCrea (5) has propounded similar ideas.

The contact time suggested by Burlingame and Reddish (9) for the fungus and test substance is 5, 15, and 30 minutes. Such long exposures are not practical, when alcohol-soluble fungicides are to be tested. A 95 per cent alcohol control was fungicidal in itself after 10 minutes contact with a 5-day-old culture. In order to make the test conditions more stringent and the results more meaningful, the contact time for alcohol-soluble fungicides has been reduced by us to 1 minute. The finer the differences in the evaluation of fungicides, the more acutely we can observe the possibilities of obtaining effective compounds.

The question will arise, "Do we need to make these finer differentiations?" If we will eventually obtain more efficient fungicides, we definitely need to put them to the severest test methods possible.

A very serious limitation of the Burlingame and Reddish (9) technique is the washing step in aqueous broth. Once again, this rinsing step is not applicable to water insoluble compounds. A simple test will convince any one of this impossibility. A 1 per cent solution of salicylic acid in 95 per cent alcohol was found to be fungicidal in 5 minutes' contact with a five-day-old culture, when tested by the original Burlingame and Reddish (9) method—that is, observing the washing step in aqueous broth. That a considerable amount of salicylic acid adhered to such a culture disk after the broth washing step was proved by a positive ferric chloride test. However, when a similar salicylic acid treated culture disk was washed for 5 minutes in a 30 per cent acetone water mixture, the substance was efficiently removed, as indicated by an almost negative ferric chloride reaction, and the final test results showed that 1 per cent salicylic acid solution is not fungicidal. At best, the Burlingame and Reddish (9) technique demonstrates a continued fungistatic rather than fungicidal action of water-insoluble compounds.

It was ascertained by us that a 30 per cent acetone-water mixture suffices in most cases to remove the adhering fungicide and that this mixture is not fungicidal in itself, even after a 15-minute contact with a 5-day-old fungus culture. Taking all of the described findings into consideration, the adoption of a modified fungicidal method gave reproducible and significant results with alcohol-soluble fungicides (18).

Testing of the Actual Antifungal Preparation

In actual therapy, fungicidal compounds are not usually dispensed in 95 per cent alcohol. We have noted that diluting down this solvent diminishes considerably the fungicidal activity of some compounds dissolved therein. For this reason, the data obtained with one concentration of the solvent may not be valid for another, and all of the reported values should be regarded merely as an expression of the relative activity of the test compound. A change or dilution of the carrier must be subjected to new tests which would furnish different values.

This brings us to the testing of the actual therapeutic antifungal preparation. What should be the concentration of the antifungal substance for clinical use? What information may be gained from

in vitro tests? Here, fungistatic tests are of very limited value. Any antifungal preparation worthy of its name should at least clear the entire test plate, if tested by the agar cup plate method in the concentrations to be used for therapy. However, very few do that. For fungicidalness, a contact time of 2 minutes in the respective carrier instead of the 1-minute with 95 per cent alcohol should be sufficient for fungicidal values. A preparation which will fulfill these test conditions will exhibit therapeutic effects with reasonable certainty. Clinical tests must then be performed to establish the absence of skin sensitizing and irritating properties.

We cannot overemphasize that favorable in vitro test results cannot always be relied on to predict accurately a favorable clinical performance by an antifungal substance. It seems that the dermatophytons which were mentioned earlier, show a definite parallel pattern in their in vitro and in vivo susceptibilities. However, if one wishes to go one step further in in vitro testing, one might culture the fungus on epidermis, on scales and the like and test their retarding effect on the antifungal substance. We do have, however, one fungus infection which because of its natural habitat lends itself excellently to this type of test, *Microsporon audouini*. Some fungicides exhibited excellent in vitro effects on the pure agar cultur of this organism, but when individual infected hairs were tested, and honestly tested, the results were quite disappointing. Most of the preparations used had excellent clinical write-ups, by the way.

We quote Dr. J. H. Mitchell, Professor of Dermatology, University of Illinois (19), who wrote:

> "Hairs taken from one infected patch of the scalp were planted on Sabouraud's medium after covering the hairs with the preparations in the following order: (1) control, (2) safety soap, (3) equal parts of phenol and camphor, (4) phenol and camphor with the addition of water, (5) Zephiran chloride, (6) Sopronol ointment, and (7) 1 per cent phenyl mercuric salicylate. All of the inoculations grew luxuriantly with the exception of those made with phenyl mercuric salicylate. Another widely advertised preparation known as 'Desenex' was tested by covering the hairs with the ointment and planting them on sabouraud agar. No attempt was made to remove the ointment from the hairs before planting. It was found that *Micro-*

> *sporon audouini* infected hairs coated with Desenex ointment will bring forth luxurious colonies of *Microsporon audouini* as if no such ointment had been applied."

Needless to say, when such a test is performed, which is at best a fungistatic test, one sometimes wonders about the excellent clinical results reported with such preparations. In the meantime, we have developed a fungistatic and fungicidal test for antifungal ointments which gives significant information (20).

In a recent evaluation of antifungal substances, Peck (21) attempts to correlate fungistatic and fungicidal action of chemicals with their tendency to stimulate fungi to produce antigens.

The substances he added produced fungistasis only, and it was found that the concentrations of Trichophytin depended on the degree of growth of the fungi. Contrary to Peck's claim this method is not measuring the effect of the fungicidal properties of chemicals. What is found may be various metabolites produced by the fungi under unfavorable growth conditions. It is not proven by any means that the allergenic substances originating from partial suppression of fungus growth are identical with those released by the sudden destruction of fungi by an actual fungicide.

The differentiation of fungistatic and fungicidal preparations may lead the clinical observer to a complete revision of thought in the evaluation of therapeutic results obtained with antifungal preparations. A fungistatic preparation will only heal over manifest skin lesions by rendering fungi into a quiescent state. After the fungistatic effect has worn off, a recurrence is most likely to happen at the very same anatomical location of the original lesion. There arises then the question of recurrence versus reinfection. We think that most of the so-called reinfections are only recurrences due to unsatisfactory and weak antifungal preparations, which are applied in high concentrations in an attempt to overcome their innate therapeutic inefficacy, which tends to perpetuate the infection and render the organisms resistant to the antifungal substance used.

Truly fungicidal preparations on the other hand would produce a different healing process on the affected skin. The manifest lesions as well as the dormant infection will be attacked by such a preparation, giving in the beginning the impression of a spreading of the skin lesions. Shedding would occur in skin areas which look apparently

normal to the superficial observer, but which harbor fungi in the resting spore stage. After the last vestiges of the infection are eliminated, a relapse could then be classified as reinfection. These preparations are also most likely to produce more intense dermatophytid reactions in sensitive persons, which may be considered another expression of their fungicidal efficacy.

Lately aliphatic fatty acid compounds have been heralded as producing cures of fungus infections. Our tests showed that most of these chemicals are only weak antifungal compounds (8, 18). Recently, it was shown by Rothman (*22*) that *Trichophytons* acquire considerable resistance to pelargonic acid, and Behrman (*23*) admits that these substances have only weak therapeutic action, confirming our test results. He suggests the search for more potent antifungal substances.

In summarizing, it may be stated that if properly performed "in vitro" tests show promising results for a chemical; one might expect some specific clinical results, but if negative results are obtained with these in vitro studies, then good clinical results are due either to unspecific influences other than an alleged antifungal potency of the investigated compound or to activation of antifungal action in vivo.

It seems that the present stage of dermatophytosis chemotherapy is comparable to the time when we treated lobar pneumonia with quinine derivatives. We have hopes that critical in vitro tests and consequent screening of compounds might in the future bring to fungus treatment what will correspond to the Sulfonamide and Penicillin level of pneumonia therapy. When this happens, we shall not have to condemn the so-called "strong fungicides" of present days which, in reality, are only extremely weak fungicides applied to the unsuspecting skin day in and day out and in horrifying concentrations. We shall then really be able to check and alter the pathological course of events which today constitutes dermatophytosis.

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COMPOUNDING PRACTICES IN THE U. S. A. AND CANADA

By Samuel W. Goldstein *

THE preliminary report of the Pharmaceutical Survey Director was given at the San Francisco Convention of the American Pharmaceutical Association in August 1948. In answer to a question as to whether the final report would contain information relative to the accuracy with which compounding is performed at the prescription-counter, Doctor Elliott stated that such a study was beyond the scope of the survey. One can readily understand that the studies of the Survey group were limited to certain correlated phases of pharmacy, and that other important studies could not be included. Nevertheless, I am sure that no one who is truly interested in pharmacy as a professional calling will challenge the need for a proper evaluation of the precision with which pharmacists are performing that function which, more than any other activity, sets them apart as professional practitioners.

A study of the compounding precision in the pharmacies of one state was reported by the author in 1947 (1). The study was made on the basis of the standards utilized in several other state surveys in order to obtain comparable data. A report (2) of the surveys in Connecticut, Florida, Maryland, and Massachusetts showed that about 59, 50, 41, and 50 per cent, respectively, of the compounded prescriptions did not meet a ± 10 per cent tolerance. Later studies (3-8) by the author showed that the 10 per cent tolerance is not a reasonable and equitable standard for all extemporaneouly compounded pharmaceuticals. A basis for the establishment of standards of tolerance for prescription-counter products has been developed, and tentative standards for liquid preparations have been determined (9, 10). A report is offered here on a nation-wide spot survey of compounding precision. The United States survey data were obtained from 951 solutions that were compounded by 446 pharmacists in 117 communities scattered throughout 47 states and the District

* Pharmaceutical Chemist, Maryland State Health Department, member of American Pharmaceutical Association Committee on Prescription Tolerances.

of Columbia. When a tolerance of ±10 per cent is applied to the assembled data, the national result is approximately the same as that which was reported for four states in 1947. About 52 per cent of the sampled solutions would be classed as acceptable. When the standards proposed in 1948 are applied to these data, about 65 per cent of the solutions are classed as acceptable. To this extent are the facts concerning compounding precision brought nearer the truth by the application of reasonable and equitable standards of tolerance.

Study of Compounding Data

Now that we have a sound and proper view of the situation, let us examine carefully the disclosed facts. A recurring criticism of reports on compounding precision is based on the presentation of insufficient data regarding the extent of the deviations beyond the working standard. That information is included in this report. The data for all the solutions utilized in this study are summarized in Tables 1 and 2. What factors are responsible for the unsatisfactory compounding of 35 per cent of all the solutions purchased? The great majority of the compounded solutions consist of 3 per cent Boric acid solution (2 ozs.) and 2 per cent Neo-Silvol solution (1 oz.). They represent the simplest type of compounded galenical in which an arithmetical calculation is required. The proposed tolerance for each solution is ±15 per cent.

Factors Affecting Precision

Is more refined equipment required for accurate compounding than that which is found in the average prescription department? In too many cases, the answer is "Yes." With respect to the solutions studied in this survey, only the simplest equipment is required. Would the use of 454, 456 grains; or 450, 437, or 500 grains per fluidounce as the basis of percentage calculations cause excessive deviation? Use of 500 grains would cause the greatest deviation of + 9.7 per cent, and use of 437 grains would cause a deviation of —4.2 per cent. The deviations caused by using the other grain weights; or by using 30 cc. and 60 cc. as equivalent volumes for 1 and 2 fluidounces, and weighing the calculated quantities with metric weights would be negligible. It would appear to be entirely reasonable to expect the deviations in these preparations to be held

Study of Compounding Precision in U. S. A. 1948-1949

TABLE 1. SUMMARY OF DATA FROM U. S. SURVEY SOLUTIONS

Solution	Number Obtained	No. of Deviations >10%	No. of Deviations >15%	No. of Deviations >20%	No. of Deviations >30%	No. of Deviations >50%
Boric acid 3% (2 ozs.)	418	211	165	139	105	55
Boric acid 3% (3 ozs.)	23	14	11	11	10	8
Neo-Silvol 2% (1 oz.)	446	193	128	94	67	36
Silver Nitrate 2% (1 oz.)	37	19	15	10	8	5
Phenol in Oil 2% (1 oz.)	27	20	14	14	11	6
Totals	951	457	333	268	202	110
Percentage of samples outside indicated limits of error		48	35	28	21	12
Omitting 55 stock (?) Boric acids solutions						
Totals	896	402	278	213	147	55
Adjusted percentage		45	31	24	16	6

within the proposed limits. The majority of the pharmacists found this to be within their abilities. Many of their products show deviations well within these limits.

Boric Acid Solution

The Boric acid solution required the larger quantity of solid and a larger volume was requested. These factors should have favored more exact products. We find, however, that a greater percentage of these solutions exceed the allowed limits of deviation than do the Neo-Silvol solutions. Of the 418 samples of 3 per cent Boric acid solution, 211 samples (50%) exceed a ±10 per cent tolerance, and 165 samples (40%) exceed a ±15 per cent tolerance. Among the 165 Boric acid solutions that exceed the 15 per cent tolerance, there appear groups of solutions that more nearly contain the amount of solute required for other unit concentrations. Eighteen samples are approximately 1 per cent; 14 samples are approximately 1.5 per cent; 21 samples are approximately 2 per cent; and 55 samples contain more than 4 per cent of boric acid. These solutions account for 65 per cent of the deviations outside the 15 per cent limits. And they all show deviations exceeding ±30%. The solutions containing more than 4 per cent of boric acid can be related to the number of pharmacists who dispensed their stock solutions of boric acid instead of the requested concentration. These are instances of dispensing errors rather than compounding deviations. Some of these pharmacists might have diluted their stock solutions, assuming that the original concentration was about 4 per cent instead of the 6 per cent solution found on some shelves. The solutions containing 1 per cent and 1.5 per cent can be related to the number of pharmacists who overlooked a multiplication in their calculations. Neglect to multiply by 3 for the percentage would yield a 1 per cent solution. Neglect to multiply by 2 for the number of ounces would yield a 1.5 per cent solution. Those who prepared a 2 per ecent solution might have been confused by the request for the 2 per cent Neo-Silvol solution at the same time. If all the erroneous Boric acid solutions that can possibly be attributed to arithmetical or ethical carelessness (108 samples) are eliminated, 103 (33%) of the remaining 310 samples do not meet a ±10 per cent limit of error, and 57 samples (18%) do not meet the ±15 per cent tolerance.

TABLE 2. GEOGRAPHIC DISTRIBUTION OF TESTED SOLUTIONS OF BORIC ACID AND NEO-SILVOL

	No. of Samples of Both Solutions Tested	Percentage of Samples Compounded Within ±10% Tolerance	Percentage of Samples Compounded Within ±15% Tolerance	Average Charge For Both Solutions	Minimum Charge	Maximum Charge
Alabama	10	40	80	.53	....	....
Arizona	9	67	67	.90	....	....
Arkansas	10	40	40	.54	.40	.60
California	31	29	45	.48	.40	.60
Colorado	30	53	63	.54	.30	.70
Connecticut [a]	16	50	75	.58	.50	.74
Delaware	20	45	70	.43	.25	.55
District of Columbia	18	55	72	.60	.40	.80
Florida [a]	33	48	61	.54	.40	.85
Georgia	10	80	80	.46	.35	.50
Idaho	10	30	50	.44	.40	.50
Illinois	22	41	50	.51	.35	.65
Indiana	20	60	75	.56	.35	.80
Iowa	20	65	80	.57	.40	.85
Kansas	19	63	84	.53	.45	.55
Kentucky	10	50	60	.40	....	....
Louisiana	10	60	90	....	....	....
Maine	7	57	71	.69	.50	.95
Maryland [a]	52	65	77	.59	.40	.80
Massachusetts [a]	31	52	65	.59	.40	.85
Michigan	20	50	60	.55	....	....
Minnesota	11	55	73	.48	....	....
Mississippi	7	71	86	.39	.30	.50

Missouri	18	44	60	.47	.25	.65
Montana	9	67	78	....	....	....
Nebraska	10	40	60	.51	.38	.70
Nevada						
New Hampshire	10	70	70	.70	....	....
New Jersey	79	52	62	.55	.30	1.00
New Mexico	10	30	50	....	....	....
New York	56	62	70	.57	.30	1.00
North Carolina	10	90	90	....	....	....
North Dakota	10	80	80	.80	....	....
Ohio	10	50	80	....	....	....
Oklahoma	14	14	22	.46	.35	.50
Oregon	22	55	64	.49	.44	.60
Pennsylvania	52	44	56	.58	.40	1.00
Rhode Island	10	10	20	.53	....	....
South Carolina	8	25	50	.27	.20	.38
South Dakota	10	80	90	.50	.50	.50
Tennessee	7	71	86	....	....	....
Texas	10	40	60	.48	....	....
Utah	10	80	90	....	....	....
Vermont	2	50	50	....	....	....
Virginia	20	50	60	.57	.30	.75
Washington	14	71	79	.59	.35	.75
West Virginia	26	58	65	.58	.35	1.00
Wisconsin	24	50	67	.68	.50	1.00
Wyoming	4	75	100	....	....	....
Summary	881	53	65	.54	.20	1.00

[a] Earlier prescription surveys showed the following percentages of samples compounded within a ±10% tolerance: Connecticut 41%, Florida 50%, Maryland 59%, and Massachusetts 50%.

The importance of the factor of mathematical confusion is further emphasized in the data obtained with 3 per cent Boric acid solutions requested in 3 ounce quantities. Six of the 23 solutions show concentrations of approximately 1 per cent. Omission of a multiplication by 3, to raise the quantity to the requested percentage or to the requested volume, could account for these solutions. Two of the solutions are approximately 2 per cent, and two pharmacists dispensed their stock N. F. Solutions. These errors all exceed ±30 per cent and account for 10 of the 11 deviations exceeding ±15 per cent. The other unsatisfactory preparation shows a deviation of 25 per cent.

The relative precision with which 2 ounces of 3 per cent Boric acid solution was compounded in different types of drugstores is indicated in Table 3. Based upon the recommended tolerance of ±15 per cent, all stores show 61 per cent acceptable samples; professional stores show 73 per cent acceptable samples; chain stores show 62 per cent acceptable samples.

Neo-Silvol Solution

The Neo-Silvol solutions were requested in 1 ounce quantities. Only one multiplication is required in the calculation, and this reduces the percentage of samples that exceed the limits of tolerance. Of the 446 samples of 2 per cent Neo-Silvol solution, 193 samples (45%) exceed a ±10 per cent tolerance, and 128 samples (29%) exceed a ±15 per cent tolerance. Among the 128 solutions considered to be unacceptable, 6 samples are approximately 1 per cent; 41 samples are approximately 3 per cent; and 12 samples contain 3.8 per cent or more of Neo-Silvol. These solutions, accounting for 46 per cent of the unacceptable solutions, show deviations exceeding ±30 per cent. Only 5 per cent of the unacceptable solutions can be attributed to neglect in multiplying by 2 to raise the quantity

TABLE 3. BORIC ACID SOLUTION 3%. PRODUCTS FROM DIFFERENT TYPES OF STORES

Type of Store	No. of Samples	No. of Deviations >±10%	No. of Deviations >±15%	No. of Deviations >±20%	No. of Deviations >±30%
All	418	211(50%)	165(40%)	139(33%)	106(25%)
Professional	47	17(36%)	13(28%)	8(17%)	6(13%)
Chain	58	31(53%)	22(38%)	22(38%)	16(28%)

to the requested percentage. The other 95 per cent of the erroneous solutions represent carelessness, confusion, or inaccurate equipment. A 3 per cent boric acid solution was requested at the same time, and that might have caused the confusion in some cases where a 3 per cent solution of Neo-Silvol was prepared. The attempt to explain how the confusion could occur should not be interpreted as an attempt to excuse the condition.

The relative precision with which the requested Neo-Silvol solution was compounded in different types of drugstores is shown in Table 4. Based upon the recommended tolerance of ±15 per cent, all stores show 72 per cent acceptable samples; professional stores show 88 per cent acceptable samples; chain stores show 70 per cent acceptable samples.

The hygroscopic properties of Neo-Silvol might affect the operator's precision to some extent, but not to such an extent that would make the 15 per cent tolerance unreasonable. Since the classification of this product as stable or unstable for purposes of standardization appeared to be debatable, a study of compounded solutions of Neo-Silvol was conducted under conditions acceptable for tolerance determinations. The results indicate that Neo-Silvol solutions can meet the tolerances determined for stable substances. Furthermore, of the 128 survey samples that show deviations greater than 15 per cent, 88 samples (69%) show plus deviations, while only 40 samples (31%) show minus deviations.

Phenol in Oil

Twenty-seven samples of 2 per cent Phenol in Oil were purchased. Six of the solutions were prepared at different times by the pharmacists in a professional pharmacy, and they bore special labels. Fourteen of the other 21 solutions carried no warning or

TABLE 4. NEO-SILVOL SOLUTION 2%. PRODUCTS FROM DIFFERENT TYPES OF STORES

Type of Store	No. of Samples	No. of Deviations >±10%	No. of Deviations >±15%	No. of Deviations >±20%	No. of Deviations >±30%
All	446	193(43%)	128(29%)	94(21%)	67(15%)
Professional	42	11(26%)	5(12%)	2(5%)	2(5%)
Chain	60	27(45%)	18(30%)	13(22%)	8(13%)

caution label. The data for the 27 samples are given in Table 5. This abbreviated study yields the following interesting and valuable information. Eleven of the 27 compounders used mineral oil as the vehicle. Four of these products contained more than 1.5 per cent of phenol, and beautiful needle-like crystals of phenol separated from solution. The crystals dissolved on warming the bottle and contents in hot tap-water, but they separated again at 25°C. No directions for warming were given. This indicates that the solubility of phenol in mineral oil has not been properly stressed. It further verifies the contention that the descriptive term "sparingly soluble" should be used for designating the solubility of phenol in liquid petrolatum.

TABLE 5. PRODUCTS DISPENSED AS 2% PHENOL IN OIL

No.	Phenol Found Gm./100 cc.	Deviation %	Oil Used	Appearance of Product
1	2.22	+11.0	Olive	Clear
2	2.47	+23.5	Mineral	Crystals
3	0.94	—53.0	Mineral	Clear
4	1.74	—13.0	Mineral	Crystals
5	2.34	+17.0	Sesame	Clear
6	1.16	—42.0	Mineral	Globule (aq.)
42	3.36	+68.0	Mineral	Layer (aq.)
43	0.84	—58.0	Mineral	Clear
44	1.09	—45.5	Olive	Clear
46	1.62	—19.0	Mineral	Red Film (aq.)
47	0.89	—55.5	Olive	Turbid (sl.)
49	0.73	—63.5	Mineral	Film (aq.)
50	1.10	—45.0	Olive	Turbid
51	0.62	—69.0	Mineral	Clear
52	1.20	—40.0	Cottonseed	Clear
53	1.02	—49.0	Olive	Turbid
69	2.01	+ 0.5	Cottonseed	Clear
70	2.13	+ 6.5	Cottonseed	Clear
71	2.54	+27.0	Cottonseed	Clear
72	2.00	0.0	Cottonseed	Clear
73	2.06	+ 3.0	Cottonseed	Clear
74	1.94	— 3.0	Cottonseed	Clear
426	1.93	— 3.5	Olive	Clear
427	1.78	—11.0	Mineral	Crystals
428	1.98	— 1.0	Olive	Clear
429	1.77	—11.5	Mineral	Crystals
430	2.48	+24.0	Olive	Clear

The U. S. P. statement that crystalline Phenol (and not Liquefied Phenol) should be used with fixed oils, liquid petrolatum, or petrolatum is important. However, it can be misleading in that it gives the impression that there is no sharp difference in the solubility of phenol in these vehicles. The word "melted" should be omtited from the U. S. P. "Note" and it should read ". . . , crystalline Phenol should be used instead of Liquefield Phenol." Apparently the melting of the phenol enables more than 1.5 per cent solubility in mineral oil with subsequent separation of phenol crystals on standing. Four of the purchased preparations showed disregard of the U. S. P. "Note" as indicated by the presence of aqueous globules in one and of an aqueous layer in another of those made with mineral oil, and by the turbidity in two of those made with olive oil. The two products, in which enough moisture was present to form only a film under the mineral oil solution, and the slightly turbid olive oil solution indicate the use of phenol which had undergone partial deliquescence.

Seven of the 27 products (26%) meet the ±10 per cent tolerance which has heretofore been used by some officials for all prescription-counter products; and 12 solutions (44%) meet the ±17.5 per cent tolerance which the proposed system of tolerance assignment indicates for this preparation. Four of the 16 solutions in which a vegetable oil was used show evidence that enough phenol was weighed to prepare a 1 per cent solution instead of a 2 per cent solution, as was requested and as the labels state. Four of the 11 mineral oil solutions might indicate the same error.

Sixteen of the solutions were obtained at professional pharmacies. The error in one of these samples was apparently caused by a mathematical oversight. Twelve of the other 15 samples fall within the ±17.5 per cent tolerance. The deviations in products obtained at different types of stores are shown in Table 6. These few results indicate that more precise work is performed in establishments con-

TABLE 6. PHENOL IN OIL 2%. PRODUCTS FROM DIFFERENT TYPES OF STORES

Type of Store	No. of Samples	No. of Deviations >±20%	No. of Deviations >±30%	No. of Deviations >±50%
Professional	16	4(25%)	1(6%)	1(6%)
Chain	6	6(100%)	6(100%)	4(67%)
Other	5	4(80%)	4(80%)	1(20%)

cerned only with professional activities. These limited data further emphasize the fact that the ±17.5 per cent tolerance recommended for solutions of this type is reasonable and is not too lenient.

Silver Nitrate Solution

Thirty-seven samples of 2 per cent Silver nitrate solution were purchased in 1 ounce quantities. Nineteen samples (51%) show deviations that exceed 10 per cent; 15 samples (41%) exceed 15 per cent; 10 samples (27%) exceed 20 per cent; 8 samples (22%) exceed 30 per cent; and 5 samples (14%) exceed 50 per cent deviations. Eleven of the solutions were dispensed in amber bottles, two in green bottles, and one in a paper-covered bottle. Three purchasers were required to sign poison registers. Five pharmacists refused to dispense the solution without prescriptions. Three of the dispensed solutions are approximately 1 per cent; three are approximately 3 per cent; one is approximately 7 per cent; and one sample contained about 1 per cent of silver proteinate instead of the labeled 2 per cent of silver nitrate.

Twenty-three of the samples have "Poison" labels, and three others are labeled "External Use Only." Four have antidote labels. Although general recognition of the unusual and dangerous characteristics of silver nitrate is evidenced by the attention given to this preparation, the precision in its compounding does not differ from that noted in the other solutions.

Labels

In recent years much has been said about the use and abuse of "catch-words" and phrases by pharmacists. The term "cut-rate" has been especially criticized and some steps have been taken to effect its removal from store-fronts. Use of the terms "Ethical Pharmacy," "Pure Drugs," "Prescriptions Properly Filled," etc., are claimed to create unfavorable impressions. The opinions regarding unfavorable publicity are expressed even when it is assumed that these phrases are used with the earnest intention of living up to them. There appear to be some instances where high-sounding "catch-words" are used only for their advertising value, with no conscious attempt to warrant their application.

While many states have not passed laws patterned after the 1938 Federal Food, Drugs, and Cosmetic Act, many of its basic

principles are accepted as necessary safeguards for the public health. Consideration of the public is the guiding principle behind the Act and the agencies enforcing it. Proper labeling for the safety of the public is one of the pharmacists many responsibilities. Even when the pharmacist can safely assume that the purchaser knows the properties and uses of a preparation he requests, the pharmacist must consider the others, not so well informed, who may have access to the dispensed product. Every solution that is dispensed for external use should carry such a notation. Among 415 Neo-Silvol solutions tested in the United States survey, the following cautioning labels appeared: "External Use Only" 29; "Shake Well" 16; "Period of Stability" 40; "Poison" 2. Labels giving sufficient information were always printed labels. Indeed it is practically impossible to place sufficient information on many drug labels unless they are printed.

The added Federal authority over prescription-counter products, indicated by the Supreme Court decision in the Sullivan case, makes a thorough review of the labeling provisions of the Federal and State drug laws imperative. The present uncertain interpretation of the acts should be clarified for the benefit of the pharmacists and the enforcement agencies. This is especially so regarding the meaning of the phrase "adequate directions." The Food and Drug Administration's interpretation has been clearly presented by Dr. Paul B. Dunbar. Among the 388 Boric acid solutions tested in the U. S. survey, the following labels appeared: "External Use Only" 23; "Poison" 1; Printed labels 22. Use of a label stating "Shake well before using" for one Boric acid solution may have been caused by a shortage of other labels. This preparation, which is frequently used as an eye wash, should be especially free from sharp particles. Several of the dispensed solutions were so concentrated that crystals of boric acid were present at 25°C. Many of the Boric acid solutions had foreign particles present.

Dispensed Volumes

Deviations of ±5 per cent in requested volumes of 2 or more fluidounces and of ±7.5 per cent in 1 fluidounce preparations have been found to be reasonable allowances. Dispensed volumes of the Boric acid and Neo-Silvol solutions, determined in more than fifty

samples, show deviations as high as plus 13 per cent and minus 12 per cent. Only 4 samples out of 52 show deviations greater than 7 per cent. It is, however, impossible to draw a general relationship between volume deviations and deviations in ingredient concentrations. Thus, one cannot state that volume deviations are generally a plus or minus factor in the observed concentration deviations. Some instances are noted where an apparent relationship exists, but no generalization can be made. The prepared volume might be measured correctly in a graduate and then incompletely transferred to the bottle. When the final volume is made up in the bottle, the deviation of the volume indicator might govern the extent of volume deviation; or, if the indicator is carelessly noted, it would have a minor influence. Careful use of any modern total-volume indicator, be it graduate or good-grade bottle mark, will generally yield a sufficiently accurate final volume.

Pricing Practices

An attempt to figure out the methods used by pharmacists to determine the prices of dispensed pharmaceuticals is very difficult. No analysis will be attempted. The facts, as noted, are reported.

The two solutions of Boric acid and Neo-Silvol were purchased in many pharmacies and drugstores. The purchase price for the two solutions ranged from twenty cents to one dollar, when requested over the counter. As prescription items, the charges were one dollar and eighteen cents, and two dollars. The Silver nitrate solutions cost twenty to thirty-five cents, when requested over the counter. One prescription request cost sixty-five cents. No general relation is observed between the prices charged and the accuracy of many of the dispensed products. However, the average charge in the professional shops is higher, and the products are generally better.

Canadian Preparations

In order to compare the compounding precision of pharmacists in Canada and the U. S. A., 101 solutions were purchased in Pharmacies in eight of the nine * Canadian provinces. Most of the purchases were made possible through the cooperation of Professor F. N. Hughes of the University of Ontario College of Pharmacy. Fifty-three

* Iceland was added later.

samples (53%) show deviations that exceed 10 per cent; 32 samples (32%) deviate more than 15 per cent; 23 samples (23%) deviate more than 20 per cent; 16 samples (16%) deviate more than 30 per cent; and 5 samples (5%) deviate more than 50 per cent.

A graphic comparison of the precision with which the pharmacists in Canada and the United States compounded solutions of Boric acid and Neo-Silvol is given in Figure 1. It is debatable

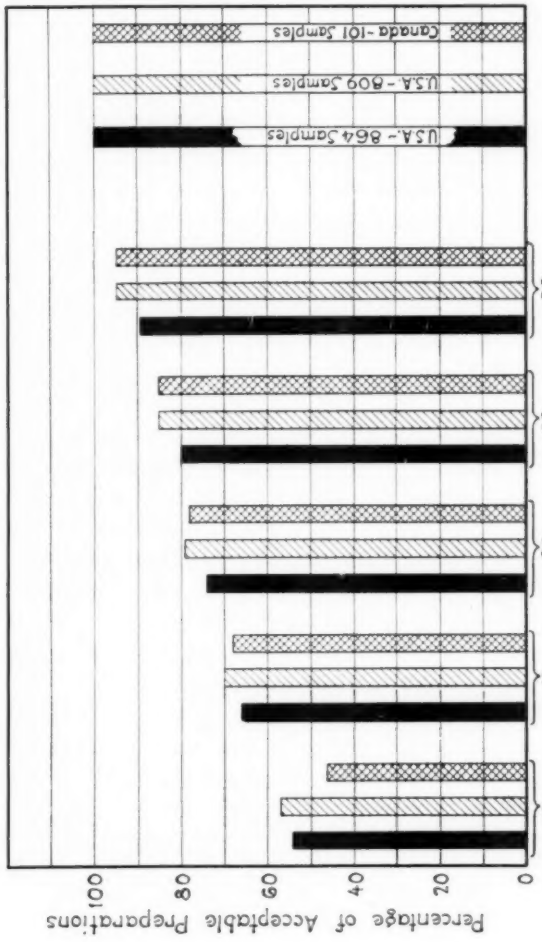

Figure 1. Relative proportions of preparations[a] compounded within indicated limits of deviation in the U.S.A.[b] and Canada.
(a) Boric Acid Solution 3 Per Cent and Neo-Silvol Solution 2 Per Cent
(b) The 864 Samples include, and the 809 Samples exclude, the 55 Samples of stock N.F. Boric Acid Solution dispensed in the U.S.A.

whether the erroneously dispensed stock N. F. Boric Acid Solutions obtained in the United States should be considered as extemporaneously compounded solutions. Two sets of figures are presented for the U. S. samples. One set includes and the other excludes the 55 samples of dispensed stock Solution of Boric Acid.

Application of the proposed tolerance of ±15 per cent shows that the compounding precision in the United States and Canada is practically the same: 66 per cent of the dispensed U. S. samples, 70 per cent of the extemporaneously compounded U. S. samples, and 68 per cent of the Canadian samples meet this standard. Practically all of the samples that exceed the ±15 per cent tolerance show such wide deviations that they cannot be classed as acceptable by any reasonable system. A larger proportion of the Canadian samples that would not be accepted by a ±10 per cent tolerance are accepted by the proposed ±15 per cent standard. In the case of the 2 per cent Neo-Silvol solution, 45 per cent of the samples meet the 10 per cent tolerance, and 67 per cent meet the 15 per cent tolerance. This represents an increase of 22 per cent in the acceptable samples. The U. S. samples of the same solution show an increase of 15 per cent in the acceptable samples. Fifty-six per cent of the U. S. samples are accepted by the 10 per cent tolerance, and 71 per cent are accepted by the 15 per cent tolerance. With the 3 per cent Boric acid solution, 50 per cent of the Canadian samples are accepted by the 10 per cent tolerance, and 70 per cent are accepted by the 15 per cent tolerance. This represents an increase of 20 per cent in the acceptable samples. Fifty per cent of the U. S. samples of the same solution are accepted by the 10 per cent tolerance, and 60 per cent are accepted by the 15 per cent tolerance. This represents an increase of 10 per cent in the acceptable samples.

Carelessness in Compounding

From the medieval period, when Paracelsus fostered iatrochemistry and the administration of specific compounds, to the present, when chemotherapy is accorded popular scientific acclaim, the practice of therapeutic druggery has been at best an empirical art. In the history of medicine, no more extensive and intensive

clinical studies are found than were reported during the development of the sulfonamides and penicillin. Yet even the valuable results of these studies have yielded knowledge which allows only approximate dosages, and these dosages are predicated upon observed approximate blood levels. However, it is a fact that blood level determinations are seldom obtained for ambulatory patients or for at-home bed patients to whom these drugs are administered by physicians. It is also a fact that marvelously effective results have been recorded in many cases in which these approximate measures have been used. The physician who prescribes an exact dosage realizes these facts, but he expects the pharmacist to dispense a preparation that will give the patient a dosage that closely approximates or is, within reasonable limits, exactly what was requested. When a layman requests a preparation containing a specified concentration of a substance, it is the pharmacist's duty to supply the exact concentration, within reasonable limits. The layman might or might not be acting on his physician's advice. But the pharmacist, in his role of protector of the public health, should exercise his utmost skill and knowledge in any and every compounding operation he is called upon to perform.

The pharmacist, as well as the physician, has been thoroughly trained in the principles of therapeutics and posology. This enables the pharmacist to render a most valuable service to both the physician and the public. He is the factor of safety between the two when he checks the prescribed dosage to ascertain that no toxic dose will be administered. But this valuable and important knowledge is allowed to operate against precise compounding in some cases. Abundant evidence has been accumulated to show that the great majority of the practicing pharmacists *can* achieve a reasonable degree of precision in their compounding. And they can do this by using the available apparatus and techniques under the prevailing conditions, if they will exercise the proper amount of care. Such care as is expected of a professionally trained individual will lead to his best and most accurate work at all times. There are still many other factors that will affect the extent of deviation in extemporaneous compounding, but control of the factor of carelessness will eliminate many of the excessive errors now noted.

Where should the pharmacist's carefulness start and what should it cover? It should start with his keeping himself fit to do precise work. It should cover his establishment and everything in it. When he orders his pharmaceutical stock, he should consider not only the economy of size of container, but also the nature of the products. Are they deliquescent, efflorescent, affected by light or air? The size and closure of the container are important. Where will they be stored to preserve their initial purity? The technical equipment must be accurate and of sufficient variety to meet all requirements. Calculations should be written and checked. If papers are placed on balance pans, the equilibrium should be checked before weighing. The many technical points that practically all pharmacists know should be kept fresh by constant application. But, most of all, the pharmacist must use his personal and technical equipment carefully.

The spectacular, and to some the unbelievable, results of this and other surveys of compounding precision should be viewed in the proper perspective. The facts prove that there is room for improvement in compounding precision. The major revelations are the frequency of, and the simple causes of excessive deviations. The desired reaction should be that we can and we must do something to improve compounding precision. There can be no doubt that the greatest single factor contributing to erroneous compounding is carelessness. The establishment and promulgation of official standards of tolerance for prescription-counter products would be a most effective educational force for carefulness.

The scientific level of pharmaceutical education has advanced greatly, along with that of the other professional groups. Some pharmacists have advanced the practical application of this newer knowledge accordingly. Many pharmacists are still practicing in the same manner and with the same apparatus and techniques that were handed down with the same drugstore for several generations. The knowledge they acquired during their academic training period was dropped in favor of expedience. The latent knowledge abounds for a great advance in professional pharmaceutical practice. Promulgation of official standards for prescription-counter products should lead to wider utilization of that latent knowledge. Perhaps it cannot be fully exploited in the various types of drugstores which now exist. There can be no doubt that more precise compounding should be

expected, and is performed, in establishments whose services to the physician and the public are limited to pharmaceutical activities. Such establishments may lead the way to the proper evaluation of pharmacy as a public health profession. Nevertheless, there are many pharmacists, practicing in all types of drugstores, who could elevate their profession, in the opinions of public health officials and physicians and in the esteem of the laity, by efficient and careful performance of those duties upon which rests their rightful and proud claim to professional recognition.

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SUBSCRIPTION NOTICE

Due to the continuing increase in costs of production, the American Journal of Pharmacy has finally been forced to raise its subscription price from $3 to $4 per year. This increase will be effective starting with the January, 1950 issue.

SELECTED ABSTRACTS

The Phenomenon of Peptic Ulcer. H. Necheles. *Am. J. Digest. Dis. 16:*237 (1949). Although the cause of ulcer is still unknown, the investigations of this phenomenon reach back for many years. The author has presented a review of many of the theories of the etiology of peptic ulcer and then has combined known facts with a number of assumptions to build a new approach to this problem.

It is known that ulcers have a predilection to the lesser curvature and pre-pyloric areas of the stomach and to the upper duodenum. It has been shown that if the end-arteries in these areas are obstructed there is a resultant anoxemia of the mucosa in this area. In the otherwise normal person this effect may result from a vagus-acetylcholine mechanism. Continuous vagus activity produces constant liberation of acetylcholine which produces continuous vasoconstriction and in turn anoxia. During anoxia the mucosa disintegrates rapidly. It has also been shown that vagus activity is increased and is almost continuous in many patients with ulcer. In light of the above the continuous activity of the vagus could produce ulcer.

The author states that the importance of hyperacidity has been overemphasized and that pepsin is not a prerequisite for the formation of peptic ulcer. Experiments with animals and observations on human beings have shown that normal or hypoacidity is present in most patients with gastric ulcer.

Another fairly well established factor in the development of ulcer is psychic disturbances. In line with this fact a number of investigators are coming to believe that the prime factor in peptic ulcer and its distress can be found in motor disturbances of the upper gastro-intestinal tract. More distress is associated with gastric tone and motility than with acidity. The author suggests that the effectiveness of alkalies in relieving ulcer distress is due more to a reduction of motility than to reduction of acidity. Vagotomy also appears to be effective in relieving the distress of peptic ulcer because of the resultant reduction of motility rather than reduction of acidity.

The author concluded that the use of such drugs as atropine and Trasentin in the treatment of peptic ulcer is valid because they

lower gastric tone and motility and also because they counteract the vasoconstrictor effects of acetylcholine. The reduction of volume and acidity of gastric secretion by these drugs is very small. If the action of these drugs could be made to be more or less continuous, the author suggests that treatment with them would be more ideal than vagotomy.

Tridione in the Treatment of Epilepsy. C. W. M. Whitty. *Brit. Med. J.* No. 4622:311 (1949). A series of 50 patients were treated with tridione (3, 5, 5-trimethyloxazolidine-2,4-dione) in an oral dosage of 0.3 to 1.8 Gm. per day. The initial adult dose was one 0.3 Gm. capsule three times a day. Children under 5 were given only one capsule a day. The dosage was then adjusted to the needs of the individual patient, but as soon as beneficial results were obtained the dose was gradually reduced to a minimum necessary to maintain the improvement. In a few cases the improvement was maintained even when the drug was stopped altogether. Of the 50 cases 22 had petit mal only, 24 had mixed grand mal and petit mal, 3 had grand mal only, and 1 had a unilateral tremor rigidity syndrome. In 31 cases the petit mal seizures were abolished or markedly reduced, and in 10 others they were reduced. Among the grand mal cases the attacks were reduced in 5 but aggravated in 10.

The author emphasizes the necessity for a constant check of the blood cell differential during therapy. Two patients, after 6 months of therapy showed a sudden marked reduction of total granulocytes. Both returned to normal within a few days. Six other patients showed a gradual but irregular reduction in granulocytes. The only other untoward effects noted were clinically minor, such as, "glare," rashes, hiccup, drowsiness, and ataxia. None required more than a temporary cessation of therapy. An important fact noted was that a sudden cessation of therapy had no tendency to cause status epilepticus in patients with grand mal—a danger which was always a possibility with barbiturates and hydantoins. The authors suggested that with increased use the greatest drawback to the use of tridione may be in its aggravations of grand mal seizures. However, the concurrent administration of sodium diphenyl hydantoinate showed promise of effectiveness when administered to patients with mixed epilepsies.

BOOK REVIEWS

Franz Berger: Handbuch der Drogenkunde Erkennung, Wertbestimmung und Anwendung. Band 1, Untersuchungsmethoden, Cortices—Flores Mit 256 Bildern, davon 162 Originale. 400 pages 1949. Verlag Wilhelm Maudrich, Wien. $10.00.

This book is written by an expert whose knowledge as a member of the committee for drug standardization and practical experience in the wholesale crude drug trade, as well as teaching activities, qualify him to write such a comprehensive book on the evaluation of crude drugs. It is the first volume in a series, covering barks and flowers only.

Modern pharmacognosy emphasizes chemical or biological evaluation rather than physical appearance of a crude drug; the book is based on this conception. The author divides his text into two parts: A general part and the monographs on specific drugs covering about 60 different barks and 62 flowers

The general part lists the different methods of drug evaluation as follows: botanical methods, physical methods, chemical methods, microsublimation, and biological methods. Microscopic analysis of powdered drugs is omitted, since there are excellent books available on this particular phase of drug evaluation.

Under botanical methods an excellent and well illustrated description of the microscope is given, explaining the optical principles.

Physical methods described are: Viscosity, capillary analysis, "foam number", determination of surface tension and fluorescence analysis.

Chemical methods describe the routine determination of ash and moisture content, extractive residue, alkaloidal content, volatile oil content and determination of tannins.

Biological methods include such determinations as bitterness, using very dilute solutions of brucine as standards, for tannins (astringency) and saponins (hemolysis).

The monographs on specific barks and flowers are preceded by an anatomical description.

This volume shows very clearly that crude drugs *per se* are used much more frequently in Continental Europe than in the United States. This book tries to impress upon the pharmacognostic expert

the necessity for an accurate evaluation of drugs in the interest of the sick. The author apologizes for not having been able to utilize the results of work carried out in other countries, since he did not have access to the foreign literature because of the war. He promises to remedy this omission in due time.

A list of references is added as well as a glossary of medical terms. This volume is a valuable addition to reference works on pharmacognosy.

E. Ehrenstein.

Chymia. Volume 2. University of Pennsylvania Press, 3446 Walnut Street, Philadelphia 4, Pa. Price: $4.00.

This book, from the Edgar F. Smith Memorial Collection of the University of Pennsylvania, is a compilation of a number of unrelated studies in the history of chemistry, with Tenney L. Davis distinguished organic chemist as editor-in-chief. Shortly after the material was assembled, Dr. Davis died, and the volume is dedicated to his memory.

Twelve papers gathered from various nations are included in the book. Certain phases of the lives of such historical characters as Sir Isaac Newton, Sir Kenelm Digby, William J. MacNeven and Wilhelm Ostwald are discussed. Early chemical laboratory instruction, seventeenth century chemists and alchemists, the history of ambergris, and early phases of the chemical atomic and molecular theory are other subjects about which a great amount of widely scattered data have been correlated into comprehensive articles. Pulvis fulminans is interestingly traced to its source by the late editor-in-chief.

Two articles by German historians are in the original German, and a chapter by a French writer is in that language. There are numerous helpful illustrations reproduced adequately by the offset process.

This volume of unusual writings and equally unusual facts would be well fitted on the book shelf of anyone interested in history, especially the history of science. An index of names to be found in this and the first Chymia, occupies 15 pages. Thus, the value of the two books as references is quite obvious.

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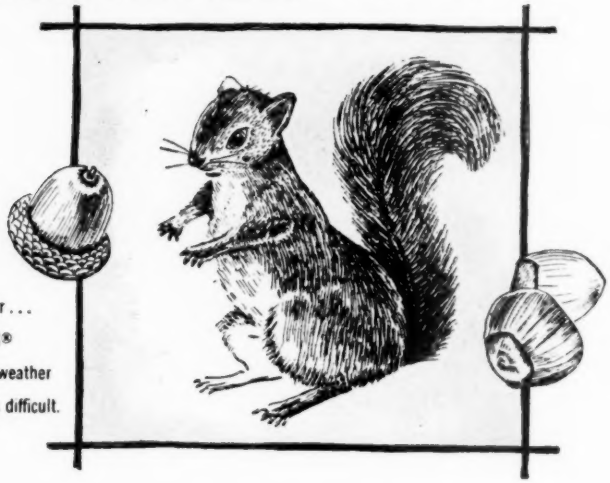

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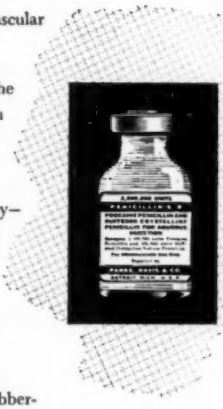

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